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ORIGINAL ARTICLE

Expression of mPGES-1 and IP mRNA is reduced by LLLT in both subplantar and brain tissues in the model of peripheral inflammation induced by carrageenan

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Abstract The increase in PGE_2 production by microsomal PGE synthase-1 (mPGES-1) in CNS contributes to the severity of the inflammatory and pain responses in the model of edema formation and hyperalgesia induced by carrageenan. PGI_2, alike to PGE_2, plays an important role in the inflammation. Low-level laser therapy (LLLT) has been used in the treatment of inflammatory pathologies, reducing both pain and the acute inflammatory process. In this work, we studied the effect of LLLT on the expression of both mPGES-1 and IP messenger RNA (mRNA), in either subplantar or total brain tissues obtained from rats submitted to model of edema formation and hyperalgesia induced by carrageenan administration. The test sample consisted of 30 rats divided into five groups: A1 (control—saline), A2 (carrageenan—0.5 mg/paw), A3 (carrageenan—0.5 mg/paw+LLLT), A4 (carrageenan—1.0 mg/paw), and A5 (carrageenan—1.0 mg/paw+LLLT). The animals from groups A3 and A5 were irradiated 1 h after induction of inflammation by carrageenan injection. Continuous-wave red laser with wavelengths of 660 nm and dose of 7.5 J/cm^2 was used. Six hours after carrageenan-induced inflammation, mPGES-1 and prostacyclin receptor (IP) mRNA expression were significantly increased both in subplantar and brain tissues. LLLT was able to reduce both mPGES-1 and IP mRNA expression in subplantar and brain tissues. We suggest that LLLT is able to reduce both inflammation and hyperalgesia observed in the model of edema formation and hyperalgesia induced by carrageenan, by a mechanism involving the decrease in the expression of both mPGES-1 and IP.

Keywords Carrageenan · IP receptor · LLLT · mPGES-1 · Peripheral inflammation

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Introduction

The classical model of edema formation and hyperalgesia induced by carrageenan administration in the rat paw has been used in the development of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors. It has been demonstrated that the increase in prostaglandin E_2 (PGE_2) production in central nervous system (CNS) contributes to the severity of the inflammatory and pain responses in this model [1]. PGE_2 is produced from PGH_2, a cyclooxygenase (COX) product, by at least three different isomerases; cytosolic PGE synthase (cPGES) and two membrane-bound PGE synthases, called microsomal PGE synthase (mPGES-1 and mPGES-2) [2, 3]. Whereas cPGES and mPGES-2 are constitutively expressed in a variety of tissues, mPGES-1, alike to COX-2, is upregulated in response to various inflammatory stimuli [3]. It has been demonstrated that mPGES-1 is closely associated with COX-2, been induced by proinflammatory stimuli both in peripheral tissues and spinal cord [4-6]. Using the model of carrageenan-induced inflammation in the rat paw, it was observed that the expression of mPGES-1 is strongly upregulated in the brain

and spinal cord during inflammation, and that the upregulation of mPGES-1 contributes to COX-2-mediated PGE_2 production in the CNS during peripheral inflammation [7]. In addition, it has been suggested that prostacyclin (PGI_2), alike to PGE_2, play an important role in the inflammation. Increased PGI_2 levels in inflamed tissue and a marked anti-inflammatory effect by prostacyclin receptor (IP) antagonist has been demonstrated, suggesting the contribution of PGI_2 in the development of chronic arthritis [8]. It was demonstrated that carrageenan administration in subplantar tissue induces the expression of IP receptor messenger RNA (mRNA) with the maximum at 6 h, coinciding to induction of COX-2 [9]. Also, intrathecal administration of the IP agonist induce mechanical hyperalgesia after carrageenan injection, suggesting that PGI_2 is involved in pain transmission at the spinal cord following expression of IP induced by peripheral inflammation [9]. Using PGI_2 receptor (IP)-deficient mice it was demonstrated an impaired acute inflammatory response in various models, including the carrageenan-induced paw edema and acetic acid induced-writhing models [10]. Low-level laser therapy (LLLT) has been used in the treatment of inflammatory pathologies, since it reduces both pain [11-15] and the acute inflammatory process [16-21]. It has been demonstrated the ability of LLLT in reduce the inflammatory responses by decrease the production of diverse inflammatory factors, including COX-2 expression and its product, PGE_2 [16-24]. Since, up-regulation of both mPGES-1 and IP presents an essential role in peripheral inflammation, in the present work; we studied the effect of LLLT on the expression of both mPGES-1 and IP mRNA, in subplantar and brain tissues obtained from rats submitted to model of edema formation and hyperalgesia induced by carrageenan administration.

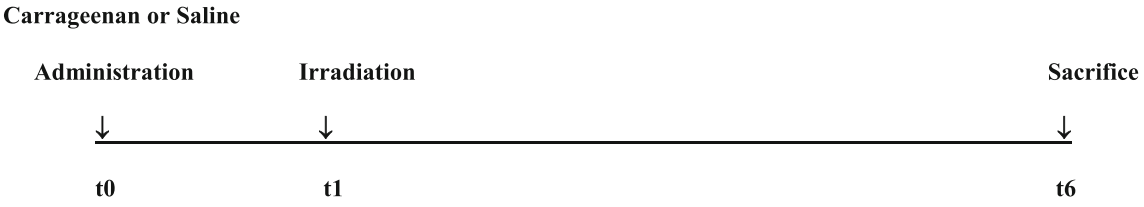
Materials and methods

Animals

All the experiments were carried according to the guidelines of the University of Vale do Paraíba for animal care. The experiments were performed using male Wistar rats (150–200 g), supplied with food and water ad libitum provided by the Central Animal House of the Research and Development Department of the Vale do Paraíba University (UNIVAP). The rats were placed in appropriate cages and randomly divided into experimental groups with six animals per group.

Experimental groups

Initially, the rats received subplantar injections (0.05 or 0.1 ml per paw) of carrageenan (Sigma Chemical Co., St Louis, MO, USA), using a stock concentration of 1 % (saline 0.85 %), in the left hind paw under brief anesthesia with halothane. Animals receiving subplantar injections of sterile physiological solution (saline) alone were included as a control group. The experiment was designed with 30 rats divided into five groups, hereafter designated as: A1 (control—saline), A2 (carrageenan—0.5 mg/paw), A3 (carrageenan—0.5 mg/paw+LLLT), A4 (carrageenan—1.0 mg/paw), and A5 (carrageenan—1.0 mg/paw+LLLT). The animals from A3 and A5 groups were irradiated at 1 h after carrageenan administration. Animals not irradiated (A1, A2, and A4) were maintained in the rest by 6 h until the sacrifice. Scheme 1 illustrates the experimental model used in this work.

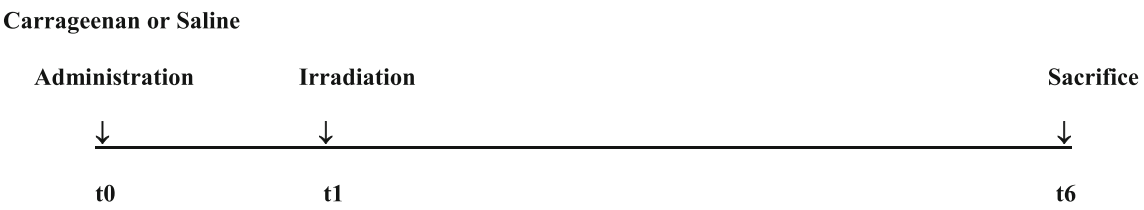


Laser irradiation

A diode laser with an output power of 30 mW and a wavelength of 660 nm (model: laser unit, Kondortech) was used. The laser beam covered an area of 0.785 cm^2, resulting in an energy dosage of 7.5 J/cm^2. The time of irradiation used was 232 s, maintaining an application distance of 1.2 cm. Spectroscopic measurements were carried out with laser, showing no thermal drift. The optical power was calibrated by using a Newport Multifunction Optical Meter (model 1835C).

RT-PCR

The animals were sacrificed 6 h after carrageenan subplantar administration and both subplantar and total brain tissues were immediately removed from the rats and stored in liquid



Scheme 1 The experimental model used in this work

nitrogen until use. Total RNA was isolated from both subplantar and brain tissues by TRIzol reagent (Gibco BRL, Gaithersburg, MD, USA), according to the manufacturer's protocol. The RNA was subjected to Dnase digestion, followed by reverse transcription to cDNA, as previously described [25]. PCR was performed in a 7000 Sequence Detection System (ABI Prism, Applied Biosystems, Foster City, CA, USA) using the SYBR Green core reaction kit (Applied Biosystems). The primers used were: rat microsomal prostaglandin E synthase-1 (mPGES-1) forward primer 5′-ATGA CTTCCCTGGGTTTGGTGATGGAG-3′ and reverse primer 5ACAGATGGTGGGCCACTTCCCAGA-3′ (GenBank accession number NM_021583); rat prostacyclin receptor (IP) forward primer 5′-AGGACTTCGATGGCAGAGGAGAC-3′ and reverse primer 5′-CAGCCCCTTACACTTCTCCAATG-3′ (GenBankTM accession number NM_001077644); β-actin forward primer 5′-AAGTCCCTCACCCTCCCAAAAG-3′ and reverse primer 5′-AAGCAATGCTGTCACCTTCCC-3′ (GenBank accession number V01217.1). The PCR primer efficiencies were calculated using standard curves, and the relative expression levels of COX-2 in real time were analyzed using the $2^{\Delta\Delta Ct}$ method, presented as the ratio to the expression of the housekeeping gene β-actin. Each sample was replicated twice from three independent sets of RNA preparations.

Statistical analysis

Statistical differences were evaluated by analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test to determine differences between groups. The results were considered significant when $P<0.05$.

Results

Effect of LLLT on both mPGES-1 and IP mRNA expression in subplantar tissue

Expression of both mPGES-1 and IP mRNA was determined in subplantar tissue obtained from animals submitted to classical model of edema formation and hyperalgesia induced by carrageenan and the results are presented in Table 1. Six hours after carrageenan-induced inflammation in rat paw, mPGES-1 mRNA expression was significantly increased in subplantar tissue, when compared to control group. Comparing to control group, it was observed an increase in the mPGES-1 mRNA expression of ~3.66-fold and ~6.91-fold, in animals receiving subplantar administration of carrageenan 0.5 and 1.0 mg/paw, respectively. The levels of mPGES-1 mRNA expression were 0.354±0.207, 1.296±0.439, and 2.445±0.874, respectively, in the control group and in groups receiving either carrageenan 0.5 or 1.0 mg/paw. The IP mRNA expression was also increased in subplantar tissue after carrageenan administration, presenting an increase in the mRNA expression of ~2.67-fold and ~5.77-fold, respectively, in animals receiving carrageenan 0.5 and 1.0 mg/paw. Expression of IP mRNA was 0.434±0.050, 1.159±0.537, and 2.503±0.738 in the control group and in groups receiving either carrageenan 0.5 or 1.0 mg/paw, respectively. The increase in both mPGES-1 and IP receptor mRNA expression presented a dose-dependent profile. Administration of LLLT (7.5 J/cm^2) reduced significantly both mPGES-1 and IP mRNA expression in animals receiving carrageenan. LLLT was able to reduce the mPGES-1 mRNA expression from 1.296±0.439 to 0.878±0.296 (~1.48-fold) and from 2.445±0.874 to 1.049±0.451 (~2.33-fold), in animals receiving either carrageenan 0.5 or 1.0 mg/paw, respectively. Following LLLT administration, the expression of IP mRNA was reduced from 1.159±0.537 to 0.520±0.269 (~2.23-fold) and from 2.503±0.738 to 1.436±0.443 (~1.74-fold), in animals receiving either carrageenan 0.5 or 1.0 mg/paw, respectively.

Effect of LLLT on both mPGES-1 and IP mRNA expression in total brain tissue

Also, the administration of carrageenan promoted a great augment in the expression of both mPGES-1 and IP mRNA in total brain tissue (Table 1). It was observed a significantly increase in the mPGES-1 mRNA expression from 0.271±0.164 to 0.929±0.224 (~3.43-fold) and from 0.271±0.164 to 1.460±0.419 (~5.39-fold), respectively, in animals receiving either carrageenan 0.5 or 1.0 mg/paw. LLLT reduced the mPGES-1 mRNA expression in ~1.26-fold and ~1.78-fold in animals receiving carrageenan 0.5 or 1.0 mg/paw, respectively. The effect of LLLT, reducing mPGES-1 mRNA expression in brain tissue was statistically significant only in animals receiving carrageenan 1.0 mg/paw. A great pronounced increase in the expression of IP receptor mRNA

Table 1 Effect of LLLT on both mPGES-1 and IP receptor mRNA expression in either subplantar or brain tissues obtained from animals receiving carrageenan in paw

	Animal group				
	A1	A2	A3	A3	A5
mPGES-1 (subplantar tissue)	0.354±0.207	1.296±0.439*	0.878±0.296	2.445±0.874*	1.049±0.451**
mPGES-1 (total brain tissue)	0.271±0.164	0.929±0.224*	0.735±0.335	1.460±0.419*	0.818±0.085**
EP2 receptor (subplantar tissue)	0.434±0.050	1.159±0.537*	0.520±0.269**	2.503±0.738*	1.436±0.238**
EP2 receptor (total brain tissue)	0.562±0.152	2.558±0.553*	1.130±0.517**	3.861±1.042*	1.573±0.438**

The experimental groups were divided into five groups: A1 (control—saline), A2 (carrageenan—0.5 mg/paw), A3 (carrageenan—0.5 mg/paw+LLLT), A4 (carrageenan—1.0 mg/paw), and A5 (carrageenan—1.0 mg/paw+LLLT). The data are mean±SE (n=6)

*P<0.05, statistical analysis indicated represents statistical analysis comparing experimental groups (A2 or A4) to control group (A1)

**Represents statistical analysis comparing experimental groups: A3 to A2 and A5 to A4

was observed following carrageenan administration in brain tissue. Expression of IP mRNA was 0.562±0.152, 2.558±0.553 and 3.861±1.042, in control group and in groups receiving carrageenan 0.5 or 1.0 mg/paw, respectively, representing an increase of ~4.55-fold and 6.87-fold. LLLT was able to reduce the IP mRNA expression values to either 1.130±0.517 (~2.26-fold) or 1.573±0.438 (~2.45-fold) in animals receiving carrageenan either 0.5 or 1.0 mg/paw, respectively.

These results show, at the first time, the ability of LLLT in decrease the expression of both mPGES-1 and IP mRNA in either subplantar or total brain tissues from animals submitted to classical model of edema formation and hyperalgesia induced by carrageenan.

Discussion

Prostaglandins are lipid mediators formed during pain and inflammation that are produced by cyclooxygenase from conversion of arachidonic acid [26]. PGH_2 is the common substrate for a number of different prostaglandin synthases or isomerases that produces a variety of biologically active mediators, including PGD_2, $PGF_{2\alpha}$, thromboxane A_2, PGE_2, and PGI_2 [6, 27]. PGE_2 and PGI_2 are the primary prostanoids involved in inflammation and inflammatory pain responses [26]. An increase in the concentrations of both PGE_2 and PGI_2 was observed following carrageenan administration in hind paw of rats, contributing to exacerbation of the inflammatory process [28]. An increase in the PGE_2 and PGI_2 concentrations was also observed in rat adjuvant-induced arthritis model [5]. The mPGES-1 produces PGE_2 from PGH_2 [2, 3], been upregulated in response to various inflammatory stimuli [3]. The results present here demonstrate an increase in the expression of mPGES-1 mRNA as in the site of inflammation as in the CNS, following carrageenan administration. These results are according to literature, indicating the evolvement of mPGES-1 in peripheral inflammation, by produce PGE_2, related to hyperalgesia at the site of peripheral inflammation. LLLT has been suggested as a new tool against inflammation; by reduce pain [11-15] and the acute inflammatory process [16-19]. Recently, it was demonstrated both antinociceptive and anti-inflammatory effects of LLLT on the inflammatory process induced in the temporomandibular joint of rodents [29]. Moreover, the potential of LLLT in attenuate the pain in patients with temporomandibular disorders has been suggested [30]. Our results demonstrated that LLLT is able to reduce mPGES-1 mRNA expression in both subplantar and brain tissues, suggesting that LLLT can reduce inflammatory process by a mechanism involving reduction in the PGE_2 release. It has been demonstrated that the expression of mPGES-1 is strongly upregulated in the brain and spinal cord during inflammation, and that the upregulation of mPGES-1 contributes to COX-2-mediated PGE_2 production in the CNS during peripheral inflammation [7]. PGI_2, alike to PGE_2, plays an important role in the inflammation. Increased PGI_2 levels in inflamed tissue and a marked anti-inflammatory effect by prostacyclin receptor (IP) antagonist has been demonstrated, suggesting the contribution of PGI_2 in the development of chronic arthritis [8]. Using PGI_2 receptor (IP)-deficient mice, it was demonstrated an impaired acute inflammatory response in various models, including the carrageenan-induced paw edema and acetic acid induced-writhing models [10]. Our results demonstrated an increase in the IP mRNA expression in animals receiving carrageenan. This increase was observed as in subplantar tissue, as in brain tissue, in a dose-dependent manner. Also, LLLT was able to decrease the IP mRNA expression both in subplantar and brain tissues. It has been demonstrated that LLLT can reduce inflammation by decrease the production of different inflammatory mediators, such as PGE_2 [16-24]. A reduction in the PGE_2 production was observed in knee inflammation induced by carrageenan after LLLT [31]. In fact, using different inflammation models it has been demonstrated by distinct authors the ability of LLLT in reduce the inflammatory process by decrease the production

of diverse inflammatory mediators [32-39]. Recently, it was demonstrated that LLLT administrated directly in the site of inflammation is able to reduce COX-2 mRNA expression in CNS and, consequently, the peripheral inflammation [40]. Presenting minimal side effects, LLLT has been presented as a very efficient tool to reduce the acute inflammation. Comparative studies with nonsteroidal anti-inflammatory drugs (NSAIDs) propose the potential of LLLT as a nonpharmacological treatment, reducing the inflammatory process [21, 23, 41, 42]. Our results indicate that LLLT administrated directly in the site of inflammation is able to reduce both mPGES-1 and IP mRNA expression both in the site of inflammation and in CNS, reducing the peripheral inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselective COX inhibitors, presenting inhibitory effect on both COX-1 and COX-2. Their side effects have been presented as a clinical limitation to the use of these drugs. Different authors have considered the inhibition of mPGES-1 as a promising new therapy by reduce the severe side effects, frequently associated to the use of NSAIDs in the therapy of inflammation, fever and pain [43-45]. Our results demonstrate evidence that LLLT can act decreasing both mPGES-1 and IP expression, decreasing the effect of both PGE_2 and PGI_2, the primary prostanoids involved in inflammation and inflammatory pain responses. It is possible that the mechanism of LLLT decreasing hyperalgesia is also related to its effect in reduce the mPGES-1 expression in CNS leading to decrease in the PGE_2 spinal cord release.

Conclusion

We suggest that LLLT is able to reduce both inflammation and hyperalgesia observed in the model of edema formation and hyperalgesia induced by carrageenan administration in the rat paw, by a mechanism involving the decrease in the expression of both mPGES-1 and prostacyclin receptor (IP).

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